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RITUXIMAB REDUCES RISK FOR RELAPSE IN PATIENTS WITH THROMBOTIC THROMBOCYTOPENIC PURPURA

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Recent systematic reviews assessing the role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura (TTP)^{1, 2} identified two major observational studies describing relapse following rituximab treatment. One report described a significantly decreased frequency of relapse in 40 patients who were treated with rituximab within three days of diagnosis, in addition to plasma exchange (PEX) and high-dose corticosteroids, compared to historical control patients who had not received rituximab.³ The other report compared 22 patients who were treated with rituximab for an inadequate response following initial treatment with PEX and corticosteroids to historical control patients who had not received rituximab; they reported no significant difference in relapse frequency related to rituximab treatment.⁴ Both studies had important limitations.¹ Control patients were retrospectively selected from a time period preceding the patient group receiving rituximab. Some patients had a history of previous episodes of TTP. Not all patients had ADAMTS13 activity less than 10%. The frequency of corticosteroid use and other treatments for TTP was not controlled. A shorter duration of follow-up of rituximab-treated patients compared to control patients potentially biased the results to observe fewer relapses in the treatment group. We updated our previous systematic review¹ to February 23, 2016 and identified no additional comparable studies of rituximab treatment for TTP.

We report the experience of the Oklahoma TTP Registry with rituximab treatment for initial episodes of acquired TTP. The Registry is an inception

cohort of all consecutive patients for whom the Oklahoma Blood Institute (OBI) is requested to provide PEX for patients with a clinical diagnosis of TTP.⁵ Since the OBI is the sole provider of PEX for all hospitals in our region, the Registry includes all patients without selection or referral bias. All identified patients have been enrolled; no patients were excluded. The Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Our report describes all 41 consecutive patients enrolled in the Registry with their first episode of acquired TTP, December, 2003 through December, 2014. The diagnosis of TTP was documented by ADAMTS13 activity less than 10%. Four (10%) of the 41 patients died with their initial episode: two were not treated with rituximab (one died before PEX began, one died during her first PEX); two were treated with rituximab (one died of *Staphylococcus aureus* sepsis; one died following failure of multiple agents). Follow-up of 36 of the 37 surviving patients is complete through 2015. One patient who was not treated with rituximab relapsed at six months and then was lost to follow-up.

Sixteen (43%) of the 37 surviving patients were treated with rituximab for their initial episode. Fourteen were treated because they were unresponsive to PEX and corticosteroids or they had recurrent thrombocytopenia when PEX was stopped. One patient was treated with rituximab because she could not return for evaluations. One patient was treated with rituximab (once) and

corticosteroids for a diagnosis of primary immune thrombocytopenia five days before TTP was diagnosed and PEX was begun; she then had three more weekly infusions. Fourteen of the 16 patients received four weekly infusions of 375 mg/m². Two patients received only one infusion, one because she developed bacteremia and one because of no insurance.

Comparison of the 16 rituximab-treated patients to the 21 patients not treated with rituximab demonstrated no significant differences in demographic features, initial clinical data, or the year of their initial episode (Table). The only differences were that rituximab-treated patients had more PEX treatments over a longer duration and received a greater total dose of corticosteroids, reflecting their inadequate response to initial treatment. Two of the 37 patients subsequently died, 16 and 30 months following TTP; neither were treated with rituximab for their TTP initial episode and neither had relapsed. Both deaths were related to systemic lupus erythematosus which preceded TTP.

The frequency of relapse among the rituximab-treated patients was significantly less than among patients not treated with rituximab ($P = 0.009$, Figure).⁶ Rituximab-treated patients relapsed at 2.5 and 9.9 years after their initial episode. Both patients had received four infusions of rituximab for their initial episode; they had ADAMTS13 activity less than 10% at the time of their relapse and they were re-treated with rituximab. Nine patients not treated with rituximab relapsed at 0.4-5.9 years (median, 3.1 years) after their initial

episode. Two of six patients who received rituximab for their initial relapses relapsed again after 3.0 and 8.6 years; they were again treated with rituximab. One of three patients who had not received rituximab for their initial relapses relapsed again after 10 months; she was then treated with rituximab. ADAMTS13 activity was less than 10% in 11 of 12 relapses; it was not measured in one. All 11 relapsing patients have survived.

Patients treated with rituximab for their initial TTP episode had significantly fewer relapses than patients not treated with rituximab, even though their initial episodes were complicated by inadequate response to initial treatment with PEX and corticosteroids. Compared to the previous reports,^{3, 4} our two groups of patients were concurrent. Only patients with their first episode of TTP were included. All patients had ADAMTS13 activity less than 10% at the time of their initial episodes. The patients' demographics, initial clinical data, and the durations of follow-up were not different. The greater total dose of corticosteroids given to rituximab-treated patients may have confounded our interpretation that rituximab was associated with the decreased frequency of relapses. Other limitations of our data are that there was no standard treatment protocol and only selected patients received rituximab. Although these patients were treated in nine different Oklahoma City hospitals, one of the authors (JNG) saw each of these 37 patients and participated in treatment decisions.

These data do not provide the strength of evidence of a randomized, controlled trial. However, since TTP is a rare disorder, it is unlikely that the effectiveness of rituximab will be studied in a randomized, controlled trial. The NHLBI Transfusion Medicine/Hemostasis Clinical Trials Network initiated a randomized, placebo-controlled trial to evaluate the efficacy of rituximab for initial treatment of patients with TTP in 2009;⁷ the trial was stopped for futility after enrollment of only three patients in the first year. The recently reported Phase 2 trial of caplacizumab for TTP⁸ also emphasizes the difficulty of conducting a randomized, controlled trial for patients with acquired TTP: 56 sites in 13 countries required 40 months to enroll 75 patients.

Although our data documented decreased frequency of relapse when rituximab was added to initial treatment with PEX and corticosteroids, we have not yet begun to use rituximab as initial treatment for all patients with TTP. Excluding the two patients who died with systemic lupus erythematosus, 10 (53%) of the remaining 19 patients whose initial episode responded promptly and completely without rituximab have not relapsed, with a median follow-up of 5.7 years (range, 2.5-9.2 years). Because we feel that patients who relapse are at greater risk for subsequent relapses, we usually treat patients who have relapsed episodes of TTP with rituximab. The values and preferences of both patients and physicians are essential for these treatment decisions.

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Author Contributions:

- Evaren Page organized and analyzed the data, created the Figure, and reviewed the manuscript
- Johanna Kremer Hovinga performed that ADAMTS13 measurements and reviewed the manuscript
- Deirdra Terrell organized the Registry protocols, maintained the IRB approvals, and reviewed the manuscript
- Sara Vesely organized the Registry protocols, supervised the data analysis, and reviewed the manuscript
- James George managed the patients, assisted with data analysis and interpretation, and wrote the manuscript

Conflicts of Interest Disclosures: The authors have no conflict of interest with the topic or data of this manuscript.

Reference List

- (1) Lim W, Vesely SK, George JN. The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura. *Blood* 2015;125(10):1526-1531.
- (2) Froissart A, Veyradier A, Hie M, Benhamou Y, Coppo P. Rituximab in autoimmune thrombotic thrombocytopenic purpura: A success story. *Europ J Int Med* 2015;26(9):659-665.
- (3) Scully MF, McDonald V, Cavenagh JD et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood* 2011;118(7):1746-1753.
- (4) Froissart A, Buffet M, Veyradier A et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. *Critical Care Med* 2012;40(1):104-111.
- (5) Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood* 2010;115(8):1500-1511.
- (6) Pintillie M. *Competing Risks: A Practical Perspective*. John Wylie and Sons; 2006.
- (7) George JN, Woodson RD, Kiss JE, Kojouri K, Vesely SK. Rituximab therapy for thrombotic thrombocytopenic purpura: a proposed study of the Transfusion Medicine/Hemostasis Clinical Trials Network with a systematic review of rituximab therapy for immune-mediated disorders. *J Clin Apheresis* 2006;21(1):49-56.
- (8) Peyvandi F, Scully M, Kremer Hovinga JA et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. *New Eng J Med* 2016;374(6):511-522.

Table 1. Comparison of 16 patients who were treated with rituximab for their initial episode of TTP to 21 patients who were not treated with rituximab, 2003-2014

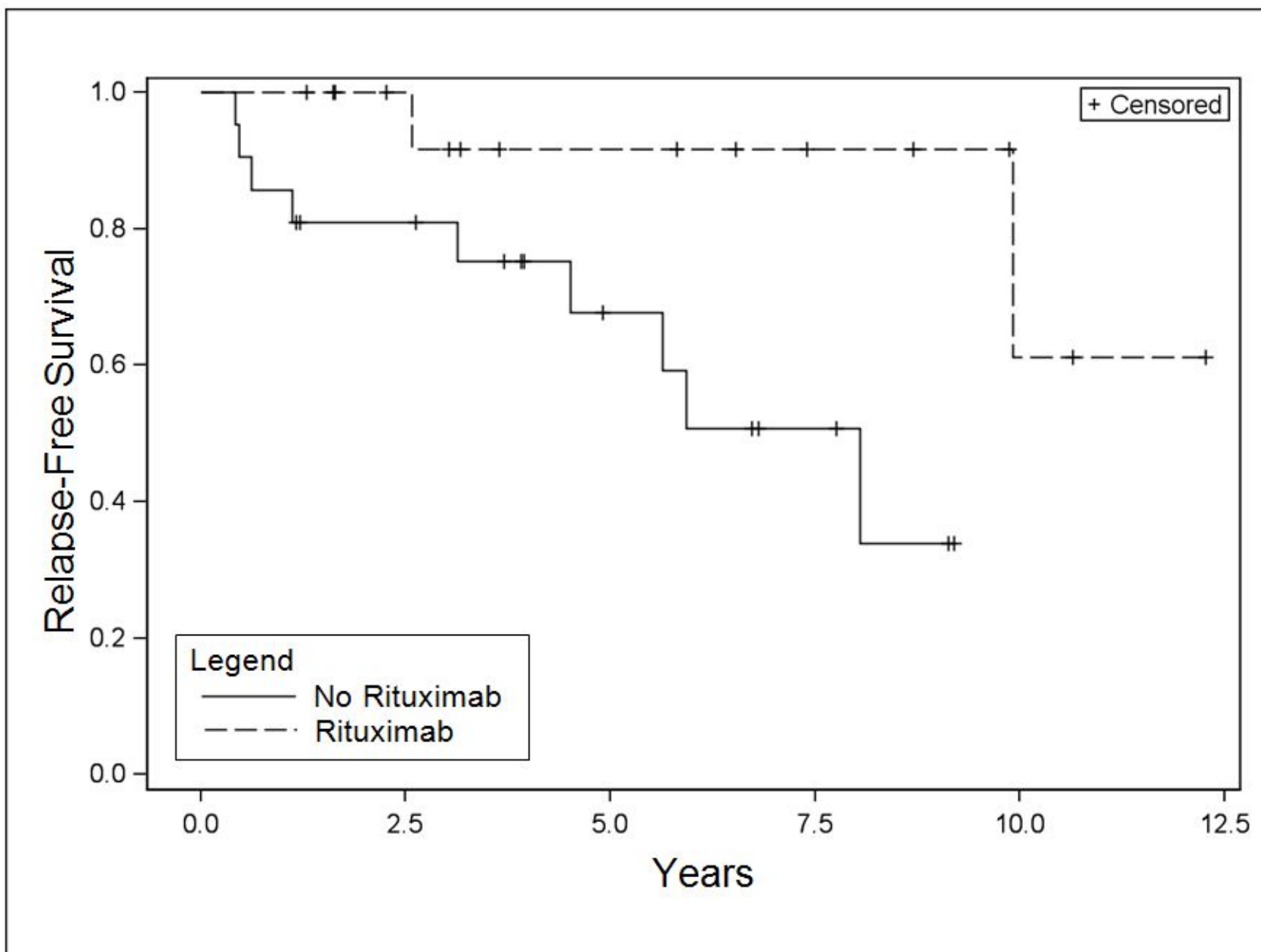
Characteristics	Rituximab	No Rituximab	P*
Patients (No.)	16	21	-
Age (median, range)	41 (20-79)	38 (18-69)	0.17
Race (No., % black)	7 (44%)	8 (38%)	0.75
Gender (No., % female)	12 (75%)	15 (71%)	1.00
Initial episode, 2009-2014 (No., %)	10 (63%)	11 (52%)	0.74
Initial clinical data			
Hematocrit (% , median, range)	22 (8-26)	21 (13-33)	0.42
Platelets (/μL x 10 ³ , median, range)	8 (5-29)	13 (4-63)	0.32
Creatinine (mg/dL, median, range)	1.5 (0.8-6.5)	1.2 (0.8-4.4)	0.12
LDH (U/L, median, range)	1206 (664-3319)	1479 (343-3519)	0.73
Severe neurologic abnormalities (No., %)	8 (50%)	11 (52%)	1.00
Treatment of initial episode			
PEX (No.)	16 (5-79)	8 (5-24)	<0.01
PEX (days from first to last PEX)	21 (5-76)	8 (5-43)	<0.01
Corticosteroid (No., %)	16 (100%)	21 (100%)	-
Corticosteroid (high-dose) (No., %)	6 (38%)	3 (14%)	0.14
Corticosteroid (total dose, mg) (median, range)	3975 (1000-14,070)	2135 (300-8870)	0.03
Cyclophosphamide	2 (13%)	0	0.18
Vincristine	1 (6%)	0	0.43

Comparison of the patients who did or did not receive rituximab for an initial episode of TTP, 2003 – 2014. This patient cohort was selected to begin with the first patient who was treated with rituximab for her refractory initial TTP episode in December, 2003. LDH (lactate dehydrogenase) values were adjusted for an upper limit of normal of 200 U/L. Major neurologic abnormalities were primarily transient focal abnormalities; seizures, stroke, and coma also occurred. The median time when rituximab was started was day 11 (day 1 is the day of the first PEX). One patient was treated with corticosteroids and one rituximab infusion for an initial diagnosis of primary immune thrombocytopenia (ITP) 5 days before TTP was diagnosed and PEX was started; she required only 5 PEX sessions; she completed the course of four weekly rituximab infusions. High-dose corticosteroid was methylprednisolone, 1000 mg/day for 3 days. The total dose of corticosteroid was calculated in prednisone equivalents for the duration of the hospital treatment of TTP. Post-hospital tapering doses of prednisone were not available.

*Median values were compared by the Wilcoxon Two-Sample Test with t approximation. The Fisher Exact Test was used for comparing proportions.

FIGURE LEGEND

Kaplan-Meier analysis of the time to relapse for 16 patients treated with rituximab and 21 patients not treated with rituximab for their initial episode of TTP. Two patients have relapsed following rituximab treatment at 2.5 and 9.9 years. Nine patients who did not receive rituximab have relapsed at 0.4-5.9 years (median, 3.1 years). Censored patients who have not relapsed at the time of their last follow-up are indicated by hash marks. Two patients not treated with rituximab and who had not relapsed died at 16 and 30 months; their deaths were related to pre-existing systemic lupus erythematosus. Hash marks do not discriminate between two patients treated with rituximab who had the same duration of follow-up (1.5 years) and two patients not treated with rituximab who had the same duration of follow-up (3.8 years). The difference was significantly different ($P = 0.009$, calculated to account for the two competing events of death).⁶





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